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CHEMOTHERAPY INDUCED HEPATOTOXICITY

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ABSTRACT

Hepatotoxicity, also known as liver damage causes the liver to under function or function irregularly. Many chemical substances or drugs are responsible for hepatotoxicity. Chemotherapy is a type of treatment that includes the medication or the combination of medications that destroys the cancer cells. These chemotherapeutic agents may cause liver damage by adding the stress to liver's filtering function and this is referred to as chemotherapy induced hepatotoxicity. Patients who are receiving chemotherapy requires close monitoring of liver function prior to treatment to know which drug is inappropriate or which drug doses have to be modified. Chemotherapeutic agents, alone or in combination, may cause hypersensitivity reactions or direct liver toxicity, and altered hepatic function and may change drug metabolism. Most cases of chemotherapy-induced hepatotoxicity are characteristic and do not have a specific clinical or histological signature that is distinct from other agents which cause hepatotoxicity. The article creates an awareness about the toxicity of every chemotherapeutic agent which is very essential before starting of new treatment to the cancer.

KEYWORDS: Hepatotoxicity, Chemotherapy, Patterns of injury.

INTRODUCTION

The largest parenchymatous organ of the body and centre for intermediate metabolism is liver. Liver has a crucial role in clearing the toxic metabolites, infectious agents and other waste products.[3] Chemotherapeutic agents which destroys cancer cells cause hepatotoxicity. Hepatotoxicity results in vascular injury, cholestasis, steatosis, fibrosis and necrosis. It is crucial to understand how various chemotherapeutic agents affect the liver. In patients with pre-existing liver disease, certain chemotherapeutic agents like vinca alkaloids, anthracyclines, taxanes, and kinase inhibitors are to be used with caution. This article reviews about how different classes of chemotherapeutic agents affect the hepatic function in patients receiving treatment with those agents.[4]

CLASSIFICATION OF CHEMOTHERAPEUTIC AGENTS AND THEIR TOXICITY ON THE LIVER

Table 1: Various chemotherapeutic agents and their mechanisms.[2]

CLASS	EXAMPLES	MECHANISM
Alkylating agents	Cyclophosphamide, Busulfan, Cisplatin, Lomustine, Chlorambucil	Inhibits DNA replication which leads to apoptosis
Antimetabolites	5- Fluorouracil, 6- MP, 6- Thioguanine, Methotrexate	Inhibits DNA replication at S-Phase of cell division
Anti-tumour antibiotics	Doxorubicin, Daunorubicin, Dactinomycin, Bleomycin, Mitoxantrone	Interferes with the enzymes required for DNA replication
Plant derivatives	Paclitaxel, Docetaxel, Vincristine, Vinorelbine	Inhibits mitosis by binding to microtubules
Immunotherapy	Interleukins, Interferons, Rituximab	Potentiates immune system to identify and kill cancer cells
Hormones	Progestin, Estrogens	Alters the production of hormones and their actions
Topoisomerase inhibitors	Topotecan, Irinotecan, Etoposide	Interferes with the enzymes required for DNA replication
Tyrosine kinase inhibitors	Erlotinib, Imatinib, Sorafenib	Inhibits tyrosine kinase

1. ALKYLATING AGENTS

Alkylating agents inhibits DNA replication which leads to apoptosis. Some alkylating agents such as chlorambucil, Cyclophosphamide, oxaliplatin can cause conditions like SOS (Sinusoidal Obstructive Disease) and VOD (Veno Occlusive Disease).[1]

Subclasses in alkylating agents include

a) Platinum compounds- Cisplatin, Carboplatin, Oxaliplatin.
b) Nitrosoureas- Carmustine, Lomustine.
c) Nitrogen mustards- Cyclophosphamide, Melphalan, Chlorambucil, Mechlorethamine.
d) Alkyl sulfonates – Busulfan.

a) Platinum Compounds

Cisplatin induced hepatotoxicity is dose related. At standard doses, cholestasis, steatosis and with minor AST (Aspartate transaminase) elevations are observed. At high doses, abnormal liver tests particularly AST (Aspartate transaminase) and ALT (Alanine transaminase) are seen.

Carboplatin (cisplatin derivative) causes hepatic injury in some patients. In some patients who administer high doses of carboplatin, they have developed autopsy documented hepatic VOD (Veno Occlusive Disease).[1]

b) Nitrosoureas

Nitrosoureas decreases the hepatic stores of glutathione and therefore results in oxidative injury. Carmustine induced liver abnormalities (elevation of liver enzymes) are reported. In some cases, elevation of ALP (Alkaline Phosphatase), AST(Aspartate transaminase) and ALT (Alanine transaminase) are reported on administration of lomustine.[1]

c) Nitrogen Mustards

When given IV, Mechlorethamine undergoes chemical changes on reaction with water or reactive compounds. Due to their rapid degradation, nitrogen mustards may not cause any liver function abnormalities.[3]

On administering Cyclophosphamide, only few cases of elevated liver enzymes are reported. In the treatment of vasculitis, administration of Cyclophosphamide followed by azathioprine, it causes liver cell necrosis.

Melphalan doesn't cause any liver damage at standard doses but it causes liver abnormalities at high doses.

Chlorambucil should be considered as a rare cause of liver damage.[1]

d) Alkyl Sulfonates

Busulfan is rarely used for myeloproliferative disorders. At standard doses, busulfan rarely causes liver damage.

2. ANTI METABOLITES

Currently using anti metabolites in cancer chemotherapy are5-Fluorouracil(5-FU), Cytosine arabinoside (ara-C), 6-Mercaptopurine(6-MP), 6-Thioguanine, Methotrexate and Gemcitabine, Fluorodeoxyuridine.

5-FLUOROURACIL

5-FU treats head, neck, breast and gastrointestinal cancers. On administering 5-FU orally, no liver damage is reported. When 5-FU is administered intravenously, there is rare chance of hepatotoxicity. When 5-FU is administered intra-arterially, hepatocellular injury with elevation of serum bilirubin, amino transferases, alkaline phosphatase and stricture of the extra or intra hepatic bile ducts together with increased bilirubin levels and alkaline phosphatase.[3] Toxicity seems to dose and time dependent. In patients undergoing treatment with 5-FU and folinic acid for colorectal metastases, CT findings showed that there is a consistent fatty change.

CYTOSINE ARABINOSIDE (ara-C) OR CYTARABINE

It is used in treating acute myelogenous leukemia. Ara-C shows cumulative dose dependent hepatotoxicity. When ara-C is given in high dose by infusing continuously over 72 hours, abnormal hepatic function tests were reported and these effects are reversible which are not dose limiting.[1] In several case reports, the administration of cytarabine showed that direct histologic evidence of hepatotoxicity which is expressed as elevated ALT levels and intrahepatic cholestasis. No treatment modifications were required unless severe drug induced hepatic cholestasis was reported.

6- MERCAPTOPURINE (6-MP)

It is used as maintenance therapy in acute lymphocytic leukaemias. Hepatocellular or cholestatic liver disease, fulminant hepatic failure resulted when the dose exceeds above 2mg/kg. Raised levels of hepatic enzymes were observed. After 30 days of beginning of therapy, episodes of jaundice is noticed and resolved after cessation of drug.[15] Early portal fibrosis is reported on prolonged therapy.[6] On conventional doses of 6-MP after liver transplantation, severe cholestasis was reported.

6-THIOGUANINE (6-TG)

It causes hepatic veno occlusive disease and hepatic vascular disease and also showed risk for nodular hyperplasia and early fibrosis.[5]

METHOTREXATE

It is used in treating breast cancer, non-Hodgkin's lymphoma, neck cancer, acute lymphoblastic leukaemia, gestational trophoblastic disease and at high doses, Methotrexate is used to treat osteosarcoma. On prolonged use, it causes hepatotoxicity, cirrhosis and

fibrosis. Increased ALT levels are dose dependent and increased with number of cycles received and it is usually temporary.[2]

3. ANTI TUMOUR ANTIBIOTICS

Anti-tumour antibodies include Doxorubicin, Daunorubicin, Mitomycin, Dactinomycin, Bleomycin and Mitoxantrone.

DOXORUBICIN

It is an Anthracycline antibiotic .On administration of doxorubicin, abnormalities in liver function tests are observed.[3] Although hepatotoxicity from doxorubicin is rare, dose reduction is suggested if the bilirubin levels are above 3.0mg/dl.

BLEOMYCIN

Because it does not cause any myelosuppression, it is used in treating squamous and testicular carcinomas and lymphomas in combination with other chemotherapeutic agents.[7] Some studies showed that there is a low incidence of liver dysfunction on the use of bleomycin.

MITOMYCIN

It also acts as alkylating agent. It may induce transient jaundice and has incriminated in veno occlusive disease.

MITOXANTRONE

Mitoxantrone is an anthraquinone antibiotic. When compared to other Anthracycline anticancer agents it shows low incidence of serious toxicities.[6] Drug produces elevations in ALT and AST levels when used in leukemic patients.

DACTINOMYCIN

Dactinomycin produces hepatotoxicity in patients who received radiotherapy involving the liver. Radiation induced hepatotoxicity prolongs the excretion and hence results in drug toxicity.[2]

4. PLANT DERIVATIVES

a) TAXANES

Paclitaxel and Docetaxel are the taxanes which comes under the class of spindle inhibitors. These act by binding to microtubules. These two drugs are mainly excreted by liver and given cautiously in individuals with hepatic impairment.

PACLITAXEL

The administration of Paclitaxel over 24 hour infusion in individuals with solid tumours and abnormal liver function resulted in increased level of bilirubin >1.5mg/dl and also associated with increased AST levels.[13] The administration of Paclitaxel over 3 hour infusion in patients with severe hepatic dysfunction resulted in increase in bilirubin above 2.0 mg/dl which confirms the incidence of toxicities to a very higher extent. Hepatic necrosis and encephalopathy are seen commonly.[14]

DOCETAXEL

The dose of docetaxel has to be decreased in individuals with moderate liver dysfunction because it resulted in high incidence of toxicity associated with the drug after the treatment.[5]

b) VINCA ALKALOIDS

VINCRISTINE

This drug is majorly eliminated by the liver but often incriminates as hepatotoxin. Following vincristine therapy there is a transient elevation of transaminases and this is greatly potentiated when used in combination with radiation. Long terms effects of such combination leads to liver fibrosis.[2] Elevations in alkaline phosphate serves as the most sensitive parameter in predicting delayed clearance and this may lead to neurotoxicity. In patients with elevated liver enzymes the treatment with Vincristine for lymphoma resulted in reactivating hepatitis.

VINORELBINE

Oral and intravenous exposure of vinorelbine does not affect the patients with moderate liver impairment (bilirubin 3.0mg/dl). In contrast, increased systemic exposure to vinorelbine resulted in high possibility of toxicity in individuals with abnormal hepatic function due to metastatic disease.[3]

5. IMMUNOTHERAPY

INTERFERONS

Recombinant α-interferons are used in treating myeloproliferative disorders, AIDS – related Kaposi's sarcoma, hairy cell leukaemia, multiple myeloma non-Hodgkin's lymphomas. At lower doses, interferons are used to treat chronic viral hepatitis. At high doses (above 10 million units/day), liver toxicity is dose limiting.[1] On administration of interferons, elevation of aminotransferases is seen but these levels get backs to normal on cessation of the drug.

INTERLEUKIN 2

Interleukin 2 is used in treating melanoma and renal carcinoma. On treating with IL-2 resulted in activating kupffer cells and initiating adhesion of leukocytes and platelets to hepatic sinusoidal epithelium and finally leads to reduction of hepatic sinusoidal blood flow.[3] In patients undergoing treatment with interferons, serum bilirubin, AST, ALT, ALP are raised and these are reversed within few days after discontinuation of therapy.[4]

RITUXIMAB

Rituximab is used in treating non-Hodgkin lymphomas of B cells. It binds to CD20 protein on surface of normal and malignant B cells results in initiation of apoptosis. Patients undergoing treatment with rituximab, hepatotoxicity and chronic hepatitis are resulted.[3]

6. HORMONES

Examples of hormones include Arimedex, Tamoxifen, Estrogens, and Progestin. Tamoxifen and Anasatrazole are used to treat breast cancer and are known to cause fatty liver disease. Postmenopausal women receiving Tamoxifen for hormone receptor positive breast cancer showed higher incidence of developing steatosis when compared to those receiving Anasatrazole. Androgens used in the breast cancer are known to carry the risk of interstitial hepatitis.[4] Hepatic adenocarcinomas were developed by the prolonged use of 17 -alkyl androgen. The use of Tamoxifen and mega sterol acetate for breast cancer and Flutamide for prostate cancer resulted in developing cholestatic hepatitis.

7. TOPOISOMERASE INHIBITORS

IRINOTECAN

Irinotecan is used in lung, Ovarian and Colorectal cancers. Steatosis and steatohepatitis are common with irinotecan therapy. When irinotecan is used before liver resection

n, steatohepatitis can increase the morbidity. A patient with elevated bilirubin and amino transferases requires dose reduction of Irinotecan.[8] There is an increased chance of neutropenia and dose restricting rise in hepatic enzymes in patients with liver impairment. Patients with Gilbert's meulengracht syndrome showed toxic levels of irinotecan due to reduction glucuronidation.[1]

ETOPOSIDE

At standard doses severe hepatic damage was reported. Veno occlusive disease was reported at higher doses.[2] Administration of etoposide at higher doses has induced hyperbilirubinemia, raised alkaline phosphatases, and elevated aminotransferases after 3 weeks. There is no change in etoposide clearance in patients with impaired liver function.[3]

8. TYROSINE KINASE INHIBITORS

Tyrosine kinase inhibitors include Erlotinib, Geftinib, imatinib, sorafenib. These agents helps to circumvent standard toxicities, while hepatotoxicity evolved as a dose restricting event.[9]

ERLOTINIB

Elevation of Grade 3-4 bilirubin was reported in patients with pre-existing moderate hepatic impairment.

GEFITNIB

It is used in the treating advanced metastatic lung cancers. Grade -3 elevation of alkaline phosphatase was reported in patients receiving this medication.

IMATINIB

Progressive elevations in liver function tests were seen in patients with solid tumours and moderate to severe liver dysfunction. Grade 3-4 Elevations of serum aminotransferases was observed in patients undergoing treatment with imatinib for chronic myeloid leukaemia.[9]

SORAFENIB

Dose restricting elevations of bilirubin occurred in patients with hepatic dysfunction and lowering of dose to half is recommended in individuals with bilirubin above 1.5mg/dl. It is not safe to use this medication in patients with bilirubin >3mg/dl.[4]

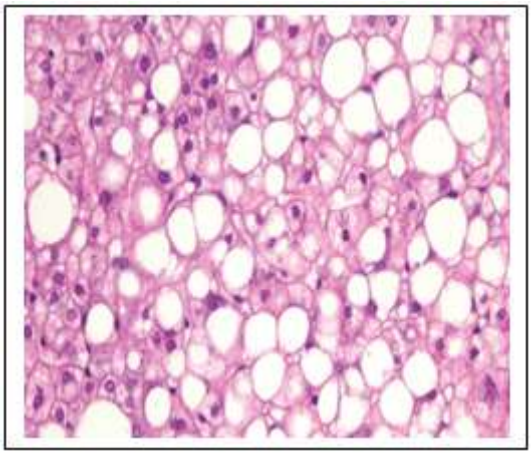

Figure-1: Simple Steatosis.

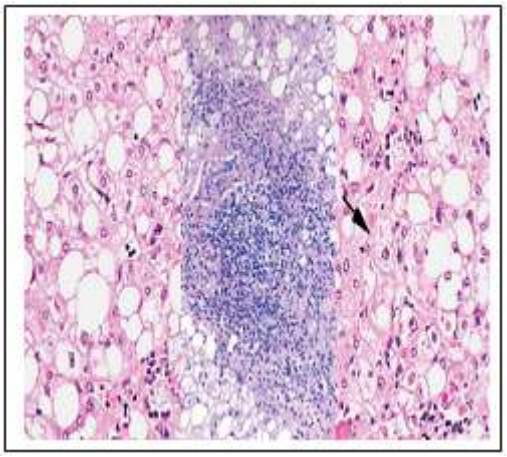

Figure-2: Hepatosteatosis.

Table no 2: Toxicity Patterns of Liver.

Hepatotoxicity Agents	Pattern	Features
Cyclophosphamide, Oxaliplatin, Vincristine,6-MP, Dacarbazine	SOS (Sinusoidal obstructive syndrome)	Fibrosis, increased bilirubin
Gemcitabine	Pseudo cirrhosis	Mimics macronodular cirrhosis
Tamoxifen, Irinotecan, Oxaliplatin	Steatosis	Fatty liver
Rituximab, Vinblastine, Cisplatin	Acute hepatitis	Elevated heptic enzymes
Methotrexate, L- Asparginase	Hepatic necrosis	Liver failure

COMBINATION THERAPY

Combination therapy involves the use of several chemotherapeutic agents which shows different toxicity profile. When 6-MP is given in combination with doxorubicin produces hyperbilirubinemia, increased levels of alkaline phosphatase and AST with each course and returns to the normal level in the middle of treatments. Some investigations showed that this is mainly due to accumulation of doxorubicin which increases the toxic effects of the other agent given in combination. In patients who are receiving combination of busulfan and 6-thioguanine for chronic granulocytic leukaemia, hepatic nodular regenerative hyperplasia was reported.[3] Fatty changes and early portal fibrosis and abnormal liver function tests were observed in children's who are receiving maintenance therapy with MTX and 6MP. Adjuvant therapy with 5-FU, MTX and cyclophosphamide for breast cancer has produced abnormal hepatic function tests. Cholestatic hepatitis was observed in patients receiving ftorafur, doxorubicin, and cyclophosphamide. Hepar lobatum has been developed in breast cancer patients receiving combination therapy. The inclusion of leucovorin to FUDR (Floxuridine) produces greater toxicity when compared to FUDR alone.[1]

When mitomycin and 5 FU are given in combination with hepatic irradiation, increase in hepatic enzymatic levels with one death was reported. Reversible hepatic steatosis was seen in patients who are receiving combination of 5FU and α interferon for metastatic colorectal cancer.[3] Tolerable doses of irradiation when combined with chemotherapeutic agents, can produce severe hepatotoxicity. When Vincristine along with abdominal radiation therapy has produced severe toxicity which is three times greater than the normal. Same combination as above when given in individuals with Non-Hodgkin's lymphoma, it produces fatal acute radiation hepatitis[2]. Radiation with doxorubicin describes the similar phenomenon of toxicity.

CONCLUSION

This article reviews about information regarding the hepatotoxicity caused by anti-neoplastic drugs. Various chemotherapeutic drugs cause liver toxicity or altered liver function. When compared to all chemotherapeutic agents Taxanes like Paclitaxel and Docetaxel are found to cause major liver damage as they are metabolised by the liver. The doses of such drugs are to be modified in patients with pre-existing liver disease.

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